Review

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Haemostatic alterations and management of haemostasis in patients with cirrhosis

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Summary

Patients with cirrhosis frequently acquire complex changes in their haemostatic system including a decreased platelet count and decreased levels of various haemostatic proteins. Although historically patients with cirrhosis were thought to have a haemostasis-related bleeding tendency, it is now widely accepted that the haemostatic system of patients with cirrhosis remains in balance as a result of simultaneous changes in pro- and anti-haemostatic systems. The concept of rebalanced haemostasis has led to changes in clinical management, although firm evidence from well-designed clinical studies is largely lacking. For example, many invasive procedures in patients with cirrhosis and a prolonged prothrombin time are now performed without prophylaxis with fresh frozen plasma. Conversely, clinicians have become more aware of the need for anti-thrombotic therapy, even in those patients with abnormal routine coagulation tests. This paper will outline recent advances in pathogenesis, prevention and treatment of both bleeding and thrombotic complications in patients with cirrhosis. Among other topics, we will discuss the haemostatic status of acutely ill patients with cirrhosis, the various causes of bleeding in patients with cirrhosis, and how best to prevent or treat bleeding. In addition, we will discuss the hypercoagulable features of patients with cirrhosis, new insights into the pathogenesis of portal vein thrombosis, and how best to prevent or treat thromboses.

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Introduction

Patients with liver disease may acquire complex alterations in their haemostatic system as the liver is the site of synthesis of many haemostatic proteins.[1] These haemostatic changes include thrombocytopenia and alterations in platelet function, low plasma levels of coagulation proteins and inhibitors of coagulation, and low levels of fibrinolytic proteins. In addition, plasma levels of proteins that are synthesised by endothelial cells, rather than hepatocytes, are frequently elevated. As both pro- and anti-haemostatic pathways change simultaneously, the net effect of the haemostatic changes in patients with cirrhosis is relatively neutral[2] (Fig. 1).

The concept of 'rebalanced haemostasis' in patients with cirrhosis is embraced by both the hepatology and haematology communities.[3,4] Although patients with cirrhosis remain in haemostatic balance, this balance is much less stable than in individuals with a healthy liver. In addition, the haemostatic profile of patients with cirrhosis has notable hypo- and hypercoagulable features which may predispose to bleeding or thrombosis.

Indeed, patients with cirrhosis may experience both bleeding and thrombotic complications, although not all of these complications are a consequence of the haemostatic alterations of cirrhosis. Some bleeding and thrombotic complications are common in patients with cirrhosis and advanced portal hypertension, including variceal bleeding and portal vein thrombosis (PVT). Deep vein thrombosis (DVT), pulmonary embolism (PE), and procedure-associated bleeding occur less commonly, but have important clinical consequences.

Unfortunately, the best strategies for prevention and treatment of bleeding and thrombosis are not fully established as we lack firm clinical data. Despite few randomised trials on haemostasis in patients with cirrhosis, there is increasing consensus on therapeutic strategies that are summarised in recent guidance documents.[3,5–7] For example, there is broad consensus on the futility of using fresh frozen plasma (FFP) with the aim to prevent spontaneous or procedure-related bleeding in patients with cirrhosis and a prolonged international normalised ratio (INR), and there is increasing utilisation of anticoagulant therapy to prevent venous thrombosis.

This review will outline recent advances in the pathogenesis and management of bleeding and thrombotic complications in patients with cirrhosis. We will specifically focus on recent breakthroughs and do not intend to give a complete overview of the field which is covered elsewhere.[8–13]

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Pathogenesis of bleeding

Key point

This paper reviews recent developments in pathogenesis, prevention, and treatment of bleeding and thrombosis in patients with cirrhosis.

The clinical observation that patients frequently bleed, either spontaneously or during major invasive procedures, has fuelled the dogma of liver disease as an acquired bleeding disorder. Although the concept of rebalanced haemostasis is broadly accepted, it remains difficult to reconcile with severe clinical bleeding complications.

The recent guidance document from the American Association for the Study of Liver Disease (AASLD) has defined 3 causes of bleeding in patients with cirrhosis[3] (Fig. 2). First, portal hypertension-related bleeding complications, such as variceal bleeding, which appear to be unrelated to haemostatic failure (based on substantial evidence). For example, it has been demonstrated that patients with acute variceal bleeding do not have a worse outcome when they are using anticoagulant drugs at the time of the bleed[14]; moreover, prohaemostatic drugs have little effect in stopping a variceal bleed.[15,16] These collective data suggest that haemostatic failure is not the primary driver of induction or propagation of a variceal bleed. Second, provoked bleeds may occur during procedures as a result of mechanical injury to vessels. Again, such bleeds are not caused by haemostatic failure *per se*, and therefore it is unlikely that prophylactic procoagulant therapy will prevent this. Third, spontaneous or unprovoked bleeds that may be related to haemostatic failure include bruising, mucosal bleeding, and oozing from puncture sites. These bleeding events are difficult to predict and are thought to be driven by underlying systemic processes. It has been proposed that prohaemostatic therapy is not a first-line therapeutic strategy in many common bleeding scenarios in patients with cirrhosis as these bleeds can be better managed by other strategies depending on the circumstances.[17]

Key point

Bleeding in patients with cirrhosis may be related to portal hypertension, to mechanical injury to vessels, or to haemostatic failure.

The haemostatic status of critically ill patients with cirrhosis

Historically, cirrhosis was classified as an acquired bleeding disorder. The combination of abnormal conventional laboratory parameters (thrombocytopenia, prolonged INR) and pervasive clinical bleeding fuelled the notion that the haemostatic changes in cirrhosis were responsible for bleeding. Variceal bleeding and bleeding during liver transplantation are common and can be dramatic. Although bleeding during liver transplantation was uniformly severe in the early days of liver transplantation,[18] even patients with profound haemostatic abnormalities can now undergo transplantation without the need for blood transfusions.[19] Variceal bleeding is primarily driven by portal pressure and not related to failure of the haemostatic system. These observations have contributed to the development of the 'rebalanced haemostasis' concept. Laboratory studies have demonstrated that acquired defects in prohaemostatic pathways are accompanied by acquired changes in anti-haemostatic pathways leading to a 'biochemical' reset in the haemostatic balance. Specifically, defects in platelet number are balanced by elevated levels of the platelet adhesive protein von Willebrand factor (VWF),[20] and decreases in procoagulant and antifibrinolytic proteins are balanced by concomitant decreases in anticoagulant and profibrinolytic proteins.[21,22] Perhaps the most notable breakthrough in the biochemical characterisation of haemostasis in patients with cirrhosis has been the use of thrombin generation assays that have been modified to include activators of the anticoagulant protein C pathway.[23] Such thrombin generation assays show normal to enhanced thrombin-generating capacity in plasma from patients with cirrhosis, despite clearly abnormal conventional coagulation tests such as the INR.[9] However, most studies have been performed in patients in a relatively stable clinical condition. Only recently have studies begun to address the haemostatic status in critically ill patients with cirrhosis (*i.e.*, those with acutely decompensated cirrhosis [AD] and acute-on-chronic liver failure [ACLF]).[11]

Fisher and coworkers provided initial evidence that the haemostatic balance in patients with AD and ACLF remains in equilibrium, despite progressive deterioration in routine haemostatic tests (platelets, INR) and levels of individual haemostatic proteins.[24] The same group subsequently confirmed and extended these findings.[25–28] Collectively, these studies confirmed that the haemostatic system remains functional even in severely ill patients. It was demonstrated that patients with AD and ACLF have highly elevated levels of the platelet adhesive protein VWF and decreased levels of the VWF-regulating protein ADAMTS13.[24,26] The VWF/ADAMTS13 imbalance is prothrombotic and may compensate for the decrease in platelet count, as has been demonstrated in patients with stable cirrhosis and patients with acute liver failure.[20,29] In addition, multiple studies have demonstrated preserved to enhanced thrombin-generating potential using plasma-based calibrated automated thrombinography.[24–26,30] Also, despite decreased fibrinogen plasma levels, the quality of fibrin clots in patients with AD and ACLF appears preserved as estimated by fluid permeation experiments.[25,26] Finally, complex changes in plasma fibrinolytic potential were shown with a hyperfibrinolytic state dominating in patients with AD, but a hypofibrinolytic state in patients with ACLF, particularly in those with sepsis.[27] The hyperfibrinolytic state in AD may be related to the fibrinolytic activity of ascites,[31] whereas in ACLF the hypofibrinolytic status may primarily be related to critical illness rather than to liver disease given the well-established

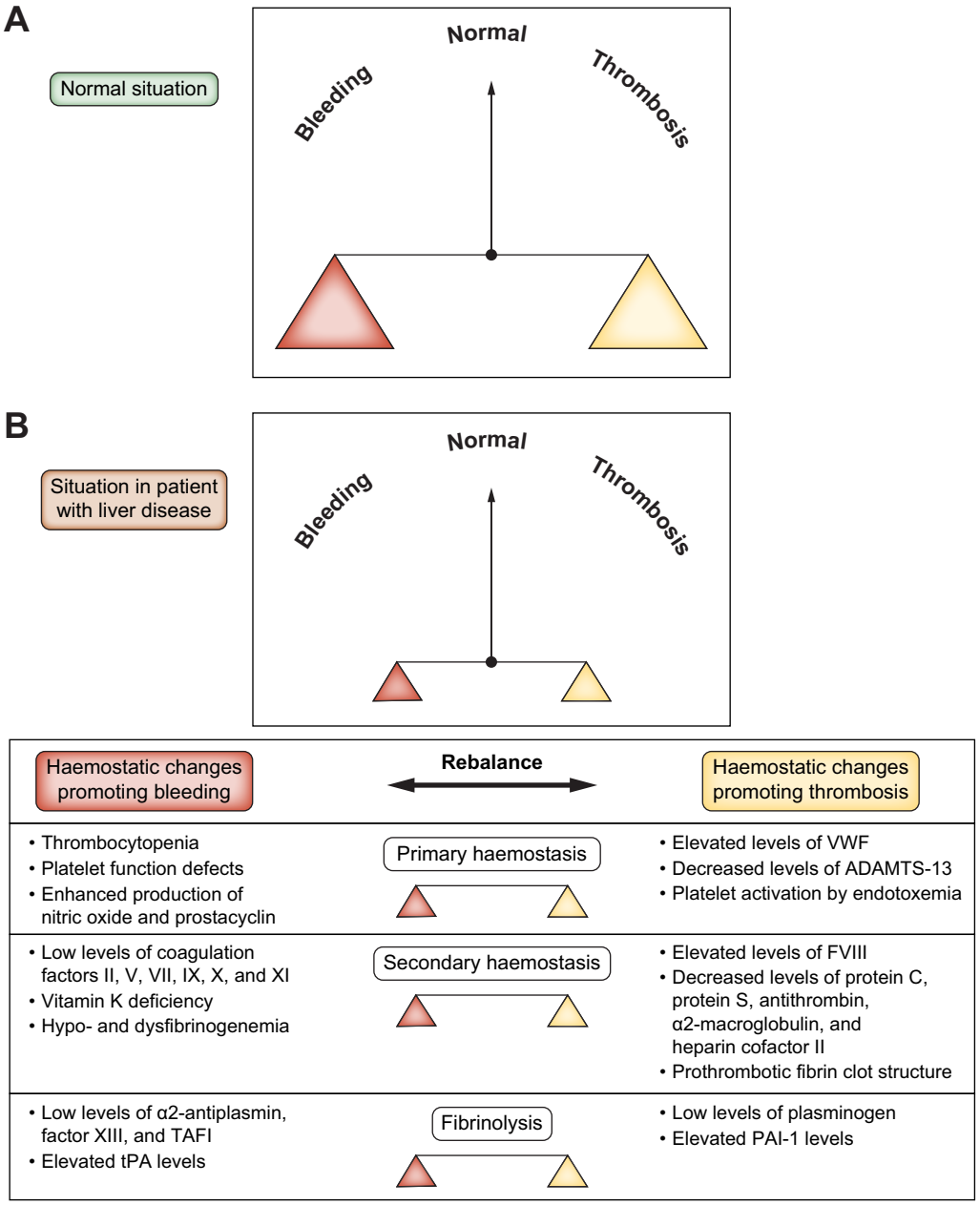

Fig. 1. Haemostatic balance in patients with liver disease. Concomitant changes in both pro- and anti-haemostatic pathways result in a 'rebalanced' haemostatic state in patients with liver disease. (A) shows the haemostatic balance in healthy individuals; (B) shows the haemostatic balance in patients with liver disease together with the individual changes in the haemostatic system. The new haemostatic balance in patients with liver disease is much less stable than the balance in healthy individuals, as there is much less weight on each end of the haemostatic scale. Simultaneous changes promoting bleeding and promoting thrombosis occur in primary and secondary haemostasis, and fibrinolysis. Modified from Curr Opin Organ Transplant 2008; 13: 298–9 with permission from Wolters Kluwer Health.[138] ADAMTS-13, A disintegrin and metalloprotease with thrombospondin-1 domain; APTT, activated partial thromboplastin time; FVIII, factor VIII; PT, prothrombin time; TAFI, thrombin activatable fibrinolysis inhibitor; VWF, von Willebrand factor.

hypofibrinolytic status in patients with sepsis but without underlying liver disease.[32] One study has compared the haemostatic profile between patients with ACLF and patients with sepsis without underlying liver disease.[26] This study showed important overlap between the haemostatic profile of patients with ACLF and patients with sepsis without underlying liver disease, suggesting that the haemostatic changes occurring in ACLF are at least partly unrelated to liver function but are rather a consequence of infection and sepsis.

Studies using whole blood viscoelastic tests performed by multiple groups came to a different conclusion and provided evidence for a hypocoagulable state in patients with ACLF.[33–35] Using 3 different technologies (thromboelastography,

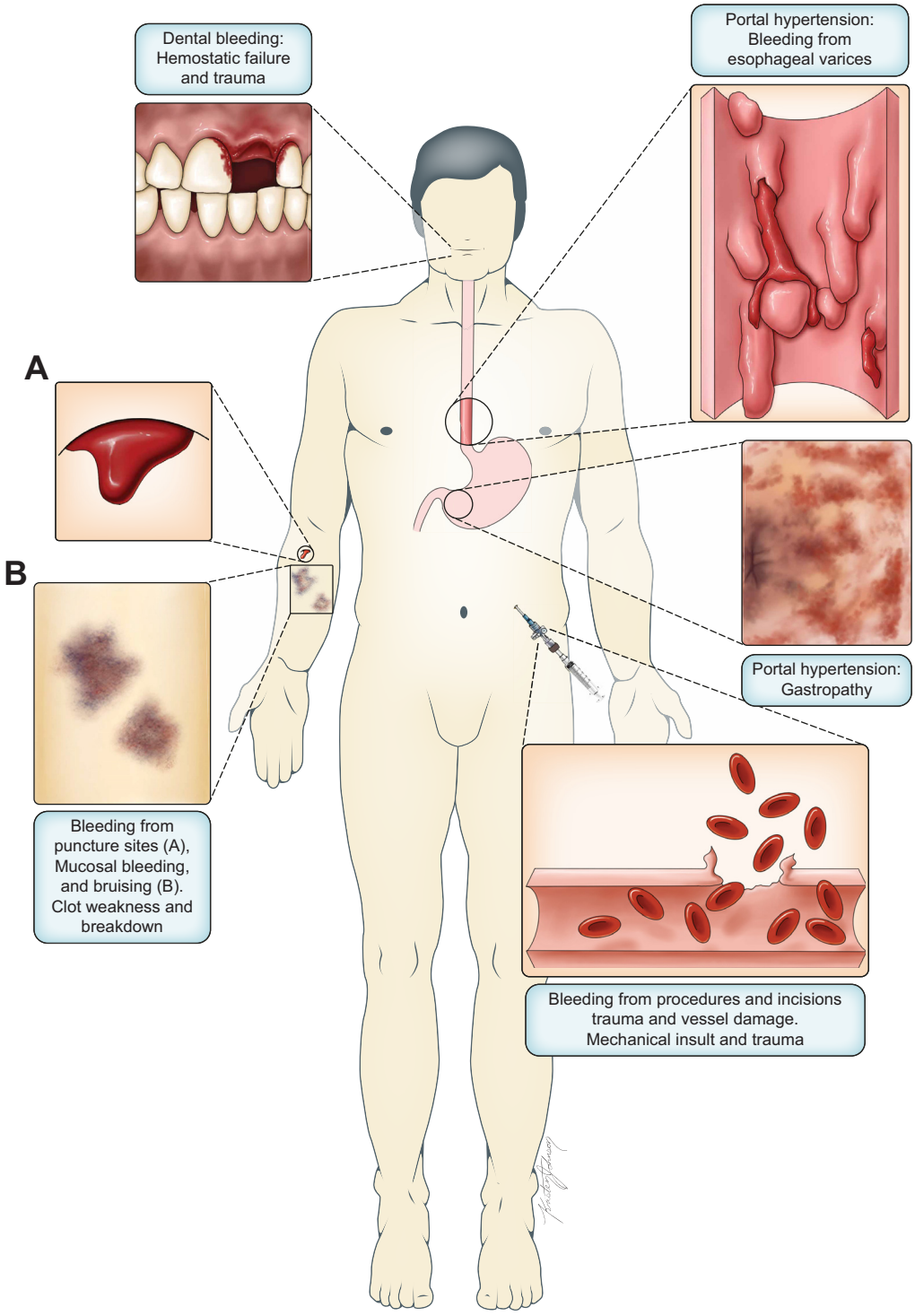

Fig. 2. Common sources of bleeding in patients with cirrhosis. Many bleeding events are due to spontaneous mechanical sources such as ruptured oesophageal varices while others are related to trauma to blood vessels and tissues, often caused by medical interventions. The minority of bleeding events are purely due to the haemostatic failure of end-stage liver disease. Figure adapted from Northup, *et al.* used with permission.[3]

rotational thromboelastometry, and sonoclot), defective whole blood clot formation (also referred to as 'coagulation failure') was demonstrated. However, as opposed to thrombin generation tests,[9] viscoelastic tests do not take the anticoagulant protein C system into account. In addition, whole blood viscoelastic tests are insensitive to the elevated levels of VWF. Both

these factors would lead to an underestimation of haemostatic capacity and may explain differences with studies using other technologies.[36]

Recent studies have demonstrated a deterioration in haemostatic profile in hospitalised patients with decompensated cirrhosis who develop acute kidney injury (AKI).[37,38] Patients who develop AKI have decreased platelet function and hyperfibrinolysis, possible related to decreased plasma levels of factor XIII. Conversely, patients with AKI had an increase in thrombin-generating capacity. Importantly, haemostatic parameters largely improved when AKI resolved.

Prevention of bleeding

Most experienced clinicians carry the indelible image of a profusely bleeding liver disease patient and may recall the rapid transition of a relatively minor procedure into a bloody debacle. These associations often prompt clinicians to intervene with prophylactic measures when caring for patients with cirrhosis. Indeed, in the intensive care unit, significantly more bleeding was demonstrated among 211 patients with cirrhosis compared to 1,493 without cirrhosis.[39] Bleeding risk was related to a disseminated intravascular coagulation score according to the definition of the International Society on Thrombosis and Haemostasis. Bleeding was particularly related to decreased fibrinogen and platelet counts. Notably, both spontaneous and procedure-related bleeding were significantly increased in critically ill patients with cirrhosis. However, many of the spontaneous bleeds were related to portal hypertension, and therefore these bleeds may have not been prevented by pro-haemostatic therapy. Notably, it is conceivable that bleeding risk may be enhanced by worsening underlying liver disease and that lower platelet counts or fibrinogen plasma levels are merely a marker of hepatic decompensation.

Strategies for prevention of bleeding or rebleeding in cirrhosis should take the 3 potential causes of bleeding (related to portal hypertension, provoked, and related to haemostatic failure) into account. Importantly, haemostatic pathways have limited involvement in portal hypertensive bleeding. Procedure-related risk is likely to be partly independent of haemostasis, but it has not been established whether prophylactic pro-haemostatic therapy reduces bleeding risk. Studies comparing prophylaxis based on viscoelastic tests *vs.* traditional coagulation testing indicate that using conventional parameters leads to significant overuse of prophylaxis without a clear reduction in bleeding.[40,41] Overall bleeding is rare and studies have been underpowered and lacked restrictive arms to understand the true baseline risk of bleeding.[42] Risk assessment of a procedure is complex, but some guidance is emerging and a multicentre prospective study assessing risk and risk factors for post-procedural bleeding in patients with cirrhosis (ProcBleed) is in progress (clinicaltrials.gov NCT04076605). Notably, common procedures like paracentesis, thoracentesis and variceal ligation are associated with a low bleeding risk and, in such cases, prophylactic procoagulant measures are unlikely to confer a benefit, as outlined in recent guidance documents.[3,7,12] Importantly, operator experience is a determinant of bleeding risk, as documented in studies on liver biopsy,[43] as is the use of image guidance (*e.g.* during catheter placement).[44] Of note, even if pro-haemostatic measures would reduce bleeding risk in certain settings, the number needed to treat would likely be substantial, even for high-risk procedures.

In clinical practice, standard laboratory tests are still frequently used to assess procedural bleeding risk in patients with cirrhosis. Whether laboratory testing has any use in this context remains controversial, and there is wide variation in the laboratory tests used to estimate bleeding risk. A solid consensus has emerged around the need to avoid using the INR and its 'correction' with FFP,[45,46] as this does not seem to increase pro-haemostatic capacity [28,47,48] and volume expansion in this setting can exacerbate portal hypertension.[49] Importantly, administration of FFP can have various other detrimental effects.[50]

Whether platelet counts or fibrinogen levels need to be corrected prior to procedures is more controversial. According to a recent meta-analysis, pre-procedural correction of platelet count by thrombopoietin receptor agonists may reduce bleeding risk, although the effect was modest.[51] Another study concluded that the benefits of thrombopoietin receptor agonists in this setting was low and these drugs are not cost effective.[52] Indeed, the recent AASLD guidance document argues against correction of the platelet count for both low- and high-risk procedures based on a lack of evidence to define a specific cut-off.[3] A recent retrospective study has suggested that increasing fibrinogen levels using cryoprecipitate does not reduce bleeding risk in critically ill patients with cirrhosis.[53] Nevertheless, we acknowledge that the haemostatic system may require support in cases of severe deficiency and that current data are not conclusive on the relationships of bleeding risk with conventional markers, such as fibrinogen and platelet count. Indeed, correction may be indicated in patients with exceptionally low levels of platelets or fibrinogen, and individualised decisions should be taken on whether to undertake restrictive or proactive pro-haemostatic management in patients with profound haemostatic abnormalities.

The procedural bleeding risks of patients with cirrhosis are genuine but the limitations of various prophylactic strategies, the relative infrequency of (severe) problems, and uncertainty around the role of haemostatic failure in some bleeding complications has led to a proposed 'rescue' approach which

Key point

Haemostatic balance in patients with cirrhosis is maintained in those with critical illness, although specific hypo- and hypercoagulable features are present.

Key point

Prophylactic administration of blood products with the aim of preventing procedural bleeding in patients with cirrhosis should not be performed routinely.

has emerged informally from past consensus meetings.[54–57] This has generally involved recommendations to optimise renal and volume status and control infection prior to procedures and to use pro-haemostatic treatment if bleeding occurs. My own bias (SC) remains to 'optimise' platelet counts to ≥50,000/ul and fibrinogen to 1.2 g/L prior to procedures associated with a higher bleeding risk.

As bleeding can be catastrophic if provoked, multidisciplinary approaches to each individual case require specific plans depending on multiple factors. Limiting unnecessary transfusions, focusing on optimising risk factors prior to procedures – such as infection, AKI, anaemia, and metabolic acidosis – and developing a plan for rescue bleeding is imperative. Future studies in this field will benefit from the more restrictive use of pre-procedure prophylaxis, which will help delineate the overall need in each particular situation. Box 1 outlines a proposed approach for prevention of procedural bleeding risk.

Key point

Pro-haemostatic therapy is not always the first-line treatment for bleeding in patients with cirrhosis.

Treatment of bleeding

Provoked and unprovoked bleeding

Many bleeds in patients with cirrhosis are not directly related to haemostatic failure, and haemostatic capacity is maintained, even in severely ill patients. Therefore, management of active non-variceal bleeds does not always require pro-haemostatic therapy. In patients with cirrhosis who are actively bleeding from a provoked source after a procedure, first focusing on local measures and/or interventional radiology procedures is essential. In patients with continuous oozing in whom local measures fail to stop the bleeding, addressing contributing factors (renal failure, infection or sepsis, and anaemia) may reduce bleeding while correction of haemostatic abnormalities can be considered on a case-by-case basis.[17] Thus, pro-haemostatic therapy is not always a first-line treatment for active bleeding. Best practices for those cases in which pro-haemostatic therapy is deemed necessary are unknown. In patients with unprovoked bleeding, such as oozing from mucosal surfaces, careful assessment of the underlying aetiology is essential. Cases with severe coagulation protein or platelet deficiency may benefit from replacement therapy and point-of-care tools such as viscoelastic tests may assist in assessment, acknowledging the aforementioned limitations. Antifibrinolytics may also have a role in certain circumstances, although they have not been studied extensively in patients with cirrhosis outside the context of liver transplantation.

Box 1. Considerations for periprocedural management of haemostasis in patients with cirrhosis

General measures

- Optimise anaemia by treating iron, folic acid, and vitamin B6 and B12 deficiencies.
- Treat infection.
- Optimise renal status.
- Avoid acidosis.
- Multidisciplinary cooperation and planning are recommended for high-risk procedures.

Haemostatic testing

- PT/INR do not predict procedural bleeding risk.
- Whether platelet count or fibrinogen levels predict procedural bleeding risk is uncertain.
- Whether viscoelastic tests predict procedural bleeding is uncertain.
- Haemostasis testing with the aim of predicting bleeding is therefore not advised. However, pre-procedure test results may be valuable as a baseline, in case bleeding does occur. In addition, haemostasis tests are indicators of disease severity.

Prophylactic administration of pro-haemostatic agents to patients with abnormal test results

- Prophylactic administration of FFP should not be performed, even in patients with highly abnormal PT/INR levels.
- Routine prophylactic administration of platelet concentrate or fibrinogen concentrate/cryoprecipitate should not always be performed.
- In patients with a highly abnormal platelet count (<20,000/μl) or fibrinogen level (<1 g/L) and/or if undergoing high-risk procedures, prophylactic administration of platelet concentrate or fibrinogen concentrate/cryoprecipitate may be performed.

Variceal bleeding

It has been well-established that acute massive variceal bleeding should be managed by endoscopic and pharmacologic therapies and with restrictive red blood cell transfusion.[58,59] Notably, transfusions of blood components, such as FFP, exacerbate portal hypertension and thus worsen bleeding. Indeed, a recent retrospective study showed that transfusion of FFP during acute variceal bleeding is ineffective and may do harm.[60,61] Specifically, in multivariable analysis, FFP transfusion was associated with an increased risk of failure to control bleeding at 5 days and with mortality at 42 days. It is tempting to speculate that FFP-induced exacerbation of portal hypertension contributed to the increased risk of failure to control bleeding in this study, whereas the combination of failure to control bleeding and potential side effects of FFP transfusion relate to increased mortality.

Tranexamic acid (TXA) is an antifibrinolytic drug that reduces mortality in bleeding patients with trauma and post-partum bleeding.[62,63] The HALT-IT trial was a placebo-controlled, randomised trial of TXA in patients with gastrointestinal bleeding.[16] A significant proportion of patients had underlying liver disease and many of the bleeds in these patients were likely variceal bleeds. This study showed that TXA did not reduce death due to bleeding but was associated with an increased risk of thromboembolic events. Similarly, recombinant factor VIIa did not confer a benefit in this setting, reinforcing the notion that pro-haemostatic therapy does not help in controlling variceal bleeding.[15,64]

The standard approach to control of variceal haemorrhage is focused on endoscopic or pharmacological measures to reduce portal hypertension.[58,65,66] Therefore, transfusions or medications aimed to improve coagulation indices or support the haemostatic system do not improve outcomes and may make the situation worse.

Post banding ulcerative bleeding is an uncommon but serious complication of band ligation for oesophageal ulcers. Studies do not demonstrate a relationship between risk of bleeding and pre-endoscopic coagulation testing.[67–70] Rather, markers of disease severity and portal hypertension (model for end-stage liver disease and Child-Pugh score) may be more predictive of risk. Management is typically based on direct endoscopic measures for control and in some indications TIPS (transjugular intrahepatic portosystemic shunt). A recent multicentre study demonstrated that administering platelets or FFP prior to endoscopic band ligation did not reduce bleeding.[70] The role of measures to support the haemostatic system in active severe bleeding remain unstudied and empirical individualised approaches are recommended.

Pathogenesis of thrombosis

It has been well-established that the haemostatic system in patients with cirrhosis has distinct hypercoagulable features, which may contribute to the risk of thrombotic complications. Specifically, a VWF/ADAMTS13 imbalance,[20,71] enhanced thrombin-generating capacity,[9] and a hypofibrinolytic status[27] are present in some patients with cirrhosis. Importantly, these haemostatic changes are known to enhance thrombotic risk in the general population.[72–76] Recent advances in this field include confirmation of a thrombotic phenotype of the fibrin clot,[77,78] and conformation of enhanced thrombin-generating capacity in patients with cirrhosis as detected with better standardised thrombin generation assays (using the Genesia device).[79,80] Animal models have suggested a role for neutrophil extracellular traps (NETs) in the hypercoagulability of cirrhosis.[81,82] It has been demonstrated that NETs mediate development of portal hypertension via thrombus formation, although the role of NETs in humans with cirrhosis has not been firmly established.[83]

Advances in our understanding of the pathogenesis of portal vein thrombosis

Very little is known about the pathogenesis of PVT and current treatment strategies are extrapolated from venous thrombosis treatment strategies.[84] Importantly, the portal venous system is not directly comparable to deep venous systems as the portal vein does not drain blood to the heart, but to hepatic sinusoids in the liver, and perhaps more importantly, the portal vein does not have venous valves,[85] which are important in the development of DVT.[86]

Some studies have suggested that a hypercoagulable state (for example factor V leiden) increases the risk of PVT development in patients with cirrhosis,[87] whereas other studies have indicated that reduced portal flow and severity of disease are important risk factors.[88–90] A recent large prospective study extensively evaluated clinical factors, the haemostatic profile, and inflammatory parameters in relation to the risk of PVT development.[88] This study showed that factors related to the severity of portal hypertension including portal flow are associated with PVT development. In contrast, inherited or acquired hypercoagulable factors and inflammatory markers did not predict PVT development. This study thus questions whether haemostatic changes have a central role in PVT development.

In line with this study, it was recently demonstrated that portal vein thrombi obtained during liver transplant surgery frequently do not contain haemostatic components such as fibrin or platelets.[91] All portal vein thrombi examined consisted of collagenised material that presents as intimal hyperplasia of the portal vein. In some patients, a true clot consisting of fibrin and platelets was present on top of this thickened intima (Fig. 3). Interestingly the fibrin-rich parts of these clots have red blood cells captured within the fibrin mesh, but these red blood cells did not have the polyhedral structure that is characteristic of red blood cells in venous and arterial thrombi. The absence of polyhedral erythrocytes within PVT clots reinforces that they are a unique entity. It was also demonstrated that portal vein intimal hyperplasia was already present in a much milder form in patients with cirrhosis without PVT, but not in healthy livers or livers from patients with acute liver failure. These results suggest that intimal thickening (and not clot formation) leads to the development of PVT (Fig. 4) and that strategies to prevent the progression of intimal thickening may be relevant for the prevention or treatment of PVT. Interestingly, activation of coagulation has an important role in intima hyperplasia in other vascular beds. Thus, although hypercoagulability and clot formation may not be central in PVT development, the activation of coagulation may play an important secondary role.

As a PVT primarily consists of intimal thickening, the term ‘portal vein thrombosis’ may be a misnomer, and ‘portal vein stenosis’ or ‘non-malignant portal vein occlusion’ may be more appropriate. These results may also explain why anticoagulant therapy frequently fails to lead to complete recanalisation, as only those portal vein thrombi with fibrin-rich sections may be susceptible to anticoagulant therapy.

Key point

Cirrhotic portal vein ‘thrombosis’ often consists of a thickened portal vein wall intima, and a fibrin-rich thrombus is frequently not present.

Prevention of thrombosis

For many years patients with cirrhosis were felt to be “auto-anticoagulated”, however, a seminal study in 2006 challenged this myth by clearly demonstrating that patients with cirrhosis develop venous thromboembolism (VTE).[92] Since this time numerous larger cohort studies have corroborated this finding and we now recognise that patients with cirrhosis are likely at increased risk of developing VTE.[93] As the development of VTE in patients

Key point

There is increasing awareness of the requirement of thromboprophylaxis in patients with cirrhosis.

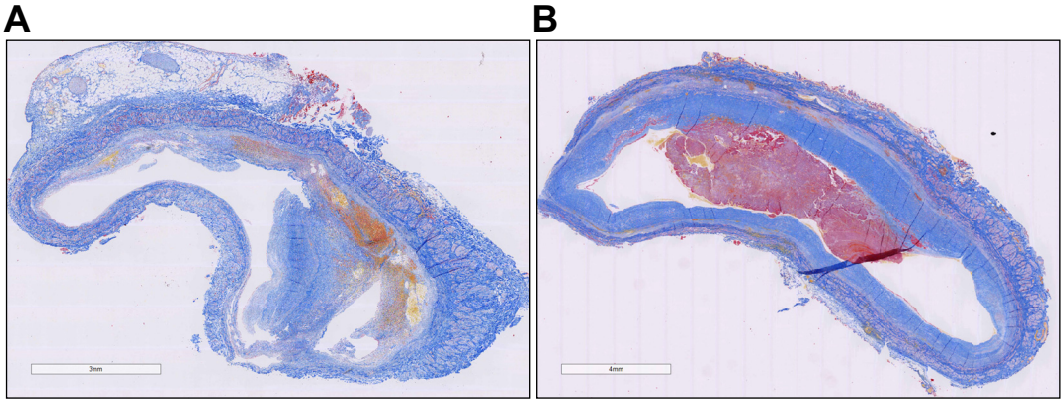

Fig. 3. Martius scarlet blue-stained sections of extrahepatic portal vein samples removed during liver transplant surgery. (A) A portal vein thrombus consisting of a focally thickened intimal layer of the vessel wall with some haemorrhage but without a fibrin-rich thrombus. (B) A portal vein thrombus consisting of a circumferential thickened intimal layer of the vessel wall with a fibrin-rich thrombus on top. Figure adapted from Driever *et al.*[91]

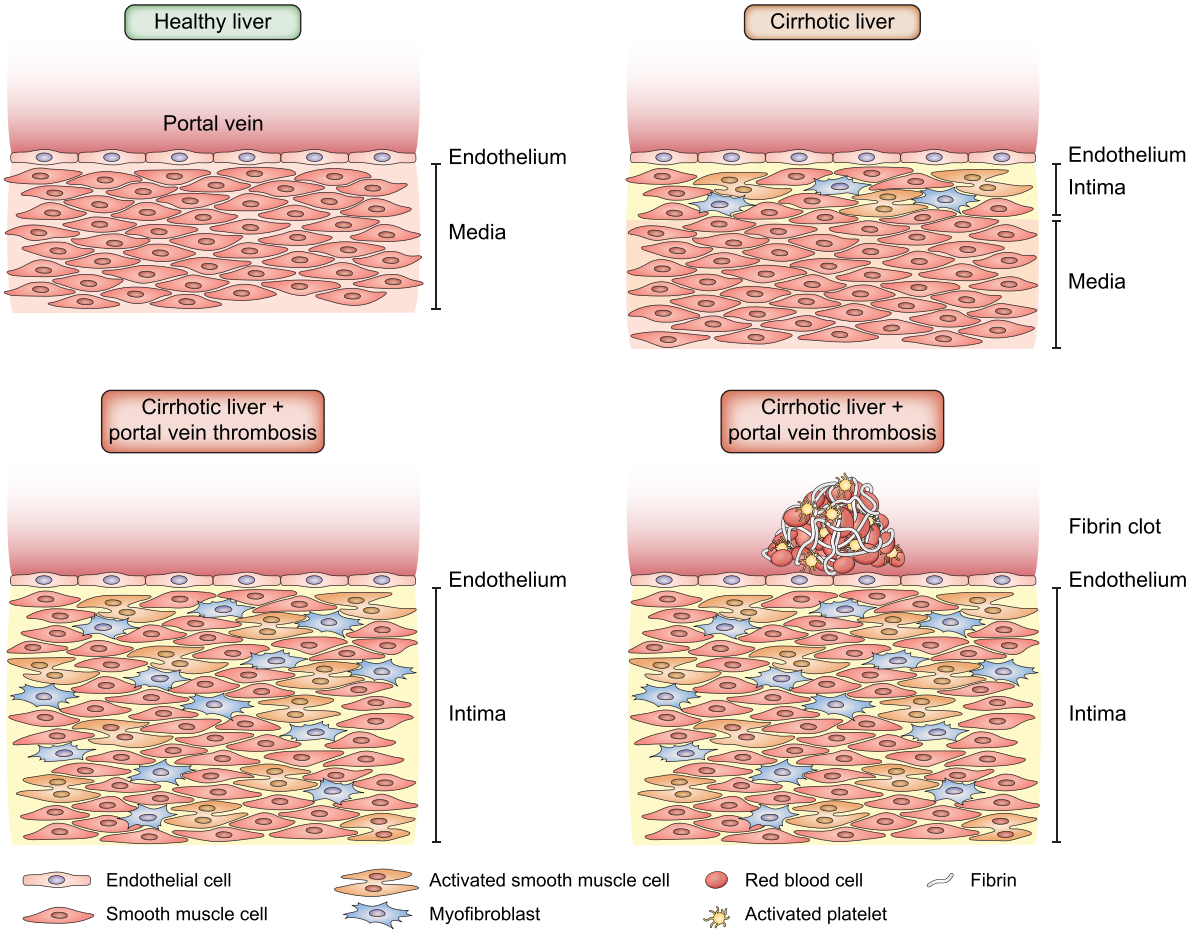

Fig. 4. Schematic overview of the role of intima hyperplasia of the portal vein in the development of cirrhotic portal vein thrombosis. The portal vein of a healthy liver lacks a detectable intima. In patients with cirrhosis, thickening of the portal vein wall is observed with an intima thickness in the order of magnitude of 200-400 um. A cirrhotic portal vein thrombus consists of a profoundly enlarged intima with a thickness of around 2 mm with or without a fibrin thrombus on top. Whether development of intimal thickening in the cirrhotic portal vein is a result of changes in blood flow (as is seen in intimal hyperplasia occurring after coronary artery bypass surgery using veins or synthetic grafts) or a result of initial clot formation with subsequent re-endothelialisation (a phenomenon previously observed in experimental venous thrombosis) requires further study.

with cirrhosis is associated with increased morbidity and mortality, prevention is highly desired.[94,95] PVT is closely associated with cirrhosis and portal hypertension. While studies have demonstrated that prevention of PVT is possible with anticoagulation, data remain sparse regarding

the practice of PVT prevention. Nevertheless, anticoagulation appears to prevent the development of PVT in patients with cirrhosis[96] and is an effective therapy to promote recanalisation in recent PVT.[97] Atrial fibrillation is a known risk factor for the development of ischaemic stroke. Patients with cirrhosis are at risk of developing atrial fibrillation and recent data in large cohorts has provided insights into the safety of direct oral anticoagulants (DOACs) in this unique population.[98]

In hospitalised patients at increased risk of thrombosis, anticoagulation is indicated to prevent the development of VTE.[99] Our understanding of the role of anticoagulation in the prevention of VTE in patients with cirrhosis remains limited, as patients with liver disease are historically excluded from clinical trials. Moreover, clinicians are often hesitant to prescribe anticoagulation to patients with liver disease owing to concerns around bleeding.[100] However in 2014, a study showed that patients with cirrhosis treated prophylactically to prevent VTE had low rates of gastrointestinal bleeding.[101] Subsequently, the use of prophylactic anticoagulation was not associated with a significant risk of bleeding in a larger cohort study.[102] To date, no study clearly demonstrates the efficacy of anticoagulation to prevent VTE and clinicians are reliant on extrapolation from medical studies in general populations.[103] Based on data from the general medical population and recent studies specific to patients with cirrhosis, current societal guidelines support the use of thromboprophylaxis in patients with cirrhosis.[3,104]

PVT occurs more frequently in patients with cirrhosis compared to the general population.[84] The most significant risk factor for the development of PVT is advanced portal hypertension and reduced portal vein velocity.[88,89] Other risk factors may include abdominal surgery, malignancy, portosystemic shunts, and aetiology of liver disease.[10] Controversy remains regarding the putative association of PVT with the development of worsening hepatic decompensation and poor outcomes.[90] Nevertheless, a considerable amount of research has accumulated on the treatment of PVT and prevention of extension or recurrence (see below). However, less is known about preventing the development of PVT in patients with cirrhosis. A seminal study was published in 2012 examining the safety and efficacy of prophylactic enoxaparin, compared to no treatment, for the prevention of PVT in patients with cirrhosis.[96] In the group who received low molecular weight heparin (LMWH) no patients developed a PVT compared to 16.6% in the group who did not receive anticoagulation. Beyond prevention of PVT, the enoxaparin group had decreased hepatic decompensation and improved survival. Current studies now seek to further evaluate the role of anticoagulation in prevention of PVT in cirrhosis (CIRROXABAN trial, clinicaltrials.gov NCT02643212). In other cohorts, such as patients with cirrhosis undergoing splenectomy, prophylactic anticoagulation reduces the incidence of PVT.[105] Given our lack of understanding of the role of screening for PVT and the unclear clinical significance of PVT, more data are needed to clarify the role, if any, of anticoagulation to prevent the development of PVT in patients with cirrhosis.

Atrial fibrillation may result in the development of ischaemic stroke in high-risk patients and anticoagulation is recommended to prevent VTE.[106] Several recent studies examined the role of warfarin and DOACs in patients with well-compensated cirrhosis.[107–112] Overall, anticoagulation appears safe and effective to prevent stroke in patients with well-compensated cirrhosis and DOACs may be safer.[103] As randomised controlled data are lacking, further evidence is needed in patients with more advanced cirrhosis to better understand the safety of anticoagulation to prevent stroke in this population.

Key point

Direct oral anticoagulants may have advantages over traditional anticoagulants in prevention or treatment of thrombosis in patients with cirrhosis.

Treatment of thrombosis

Over recent years, the medical treatment options for thrombosis have grown tremendously with the advent of DOACs. Comprehensive knowledge of the risks and benefits of traditional anticoagulation (LMWH and vitamin K antagonists [VKA]) and DOACs can now be used to guide treatment for VTE in most patients. However, patients with liver disease are routinely excluded from clinical trials studying anticoagulation; therefore, our understanding of the safety and efficacy of these treatments in patients with cirrhosis remains limited. Nevertheless, patients with cirrhosis often develop venous thrombosis including DVT, PE, and PVT. Treatment requires a thorough understanding of the unique aspects of the haemostatic system described above and each drug has risks and benefits particular to patients with cirrhosis (Table 1). As the liver and kidneys play key roles in drug metabolism, the pharmacokinetics of anticoagulants may be different, particularly in advanced liver disease. In addition, data from *in vitro* studies have identified important alterations in the anticoagulant capacity of commonly used drugs.[113–116] In these important studies, investigators used thrombin generation assays to measure the anticoagulation potency of traditional anticoagulation and DOACs. In one study, the potency of anticoagulation differed significantly between drugs and depending on degree of hepatic decompensation.[116] Dabigatran demonstrated significantly increased potency in more advanced cirrhosis whereas rivaroxaban had decreased potency. The first detailed pharmacokinetic study in patients with cirrhosis analysed the plasma after repeated doses of edoxaban.[117] Compared to healthy controls, drug levels were similar in patients with cirrhosis, however the anticoagulant effect was reduced, as measured by *ex vivo* thrombin generation tests and reduction in d-dimer level.

Table 1. Characteristics of anticoagulant drugs and their use in patients with cirrhosis.

Anticoagulant	Mechanism	Dosing recommendation in cirrhosis^	Excretion	*In vitro* studies in cirrhosis assessing potency[1]	Clinical studies in cirrhosis
Unfractionated heparin	Binds to AT indirectly inhibits Xa and IIa	Not specified	Reticulo-endothelial systems, Urine (dose-dependent mechanisms of excretion)	No significant change potency according to Child-Pugh	Case series Cohort studies
Low molecular weight heparins	Binds to AT indirectly inhibits Xa	"Caution advised in hepatic impairment"	Urine 40%	No significant change potency according to Child-Pugh	Case reports/series Cohort studies Randomised controlled trial
Warfarin	Inhibits vitamin K dependent coagulation factors	Warning in "moderate to severe hepatic impairment"	Urine 92%	None	Case reports/series Cohort studies
Dabigatran	Inhibits factor IIa	Child-Pugh A- Not specified Child-Pugh B- Not specified Child-Pugh C- Not specified	Urine primarily	Increased potency in Child-Pugh A/B/C cirrhosis	Case reports/series Cohort studies
Rivaroxaban Apixaban Edoxaban	Inhibit factor Xa	Child-Pugh A- No adjustment Child-Pugh B- Caution/Avoid Child-Pugh C- Avoid	Urine 66%/ faeces 28% Urine 27%/ faeces 73% Urine 50%/ faeces 50%	Decreased potency in Child-Pugh A/B/C cirrhosis	Case reports/series Cohort studies Randomised controlled trial*

AT, antithrombin; PVT, portal vein thrombosis.
1[115–117]

*Studies assessing PVT in patients with cirrhosis.
^Based on FDA package inserts.

Key point

There is a clear need for well-designed prospective clinical trials to obtain high-quality evidence for best management practices to prevent or treat bleeding and thrombosis in patients with cirrhosis.

Much of our understanding of the safety and efficacy of anticoagulation for venous thrombosis in patients with cirrhosis has arisen from studies in patients with PVT. Two early studies examined treatment of PVT using VKA[118] and LMWH[119] in patients with cirrhosis and showed substantial rates of portal vein recanalisation and low risk of bleeding. Subsequently a seminal study was published in 2012 which examined the effect of anticoagulation (LMWH or VKA) in 55 patients.[120] In this cohort a complete or partial response to therapy was achieved in 60% of patients with low rates of bleeding due to anticoagulation. Now these findings have been reproduced in a wide variety of cohorts.[121–128] A recent systematic review found that 64% of patients treated with anticoagulation (LMWH or VKA) undergo recanalisation compared to 21% who do not receive anticoagulation, with similar rates of overall bleeding between groups.[103] However, these studies are limited by their retrospective (non-randomised) designs, and variations in outcome definitions and durations of treatment. Current guideline recommendations support the use of anticoagulation for treatment in patients with cirrhosis and acute or recent PVT without contraindications.[3] Beyond medical therapy for PVT, TIPS is emerging as a very effective treatment for both recent PVT and in certain circumstances chronic PVT.[129–131]

The use of DOACs has proliferated in recent years owing to many attractive features including ease of use, oral administration, and there being no requirement for monitoring or dietary adjustments (see Table 1). However, clinical data in patients with cirrhosis, particularly advanced cirrhosis, was initially lacking. Manufacturers do not recommend the use of most DOACs in patients with Child-Pugh B or C cirrhosis. An initial series of patients with cirrhosis treated with DOACs for a variety of indications was reported in 2016.[132] When comparing patients treated with DOACs to a similar cohort treated with traditional agents, there were similar rates of bleeding events. Subsequent studies corroborated these findings.[133,134] A recent systematic review of 7 studies including 683 patients found no significant difference in major bleeding rates between patients who received DOACs or traditional anticoagulants.[135] However, more recently, experience with DOAC use in patients with Child-Pugh B/C cirrhosis reveals increased bleeding rates in patients with advanced cirrhosis.[136,137] Therefore, caution is required when using DOACs in patients with cirrhosis and further studies are needed.

As the paradigm of the rebalanced haemostatic system in cirrhosis is now established, our understanding of the role of anticoagulation has advanced significantly. Through studies of anticoagulation in PVT we are beginning to more clearly understand safety and efficacy profiles which may be extrapolated for use in other indications. Future research is needed to define safety profile, proper dose adjustment, and efficacy more clearly for all anticoagulants in this unique patient population.

Conclusion

We have learned a great deal on the consequences of haemostatic changes in patients with

cirrhosis in the last 20 years. Although high-quality clinical evidence is largely lacking, we have moved to a much more rational approach to management of bleeding and thrombotic complications in these patients. Herein, we have described recent advances in pathogenesis, prevention, and treatment of bleeding and thrombosis in patients with cirrhosis. Although there have been exciting advances in this field, large, well-designed, prospective trials are urgently needed to provide the high-quality evidence required to define best practices.

Abbreviations

AASLD, American Association for the Study of Liver Disease; ACLF, acute-on-chronic liver failure; AD, acute decompensation of cirrhosis; AKI, acute kidney injury, DIC, disseminated intravascular coagulation; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; FFP, fresh frozen plasma; INR, international normalised ratio; LMWH, low molecular weight heparin; NET, neutrophil extracellular trap; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt; TXA, tranexamic acid; VKA, vitamin K antagonist; VTE, venous thromboembolism; VWF, von Willebrand factor.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

TL, SHC, and NMI drafted individual sections of the manuscript and all authors revised each other's sections.

Supplementary data

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Author names in bold designate shared co-first authorship

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